Efficient Treatment of Out-of-Plane Bend and Improper Torsion Interactions in MM2, MM3, and MM4 Molecular Mechanics Calculations

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Received 27 September 1996; accepted 1 June 1997

ABSTRACT: Simple and very efficient formulas are presented for four-body out-of-plane bend (used in MM2 and MM3 force fields) and improper torsion (used in the MM4 force field) internal coordinates and their first and second derivatives. The use of a small set of bend and stretch intermediates allows for order of magnitude decreases in calculation time for potential energies and their first and second derivatives, which are required in molecular mechanics calculations. The formulas are eminently suitable for use in molecular simulations of systems with complicated bond networks. © 1997 John Wiley & Sons, Inc.* *J Comput Chem* **18**: 1804–1811, 1997

Keywords: molecular mechanics; geometric statement function method; in-plane and out-of-plane bend; improper torsion; MM2, MM3, and MM4 force fields

Introduction

The classical dynamics and energetics of potential energy surfaces may be studied by molecular dynamics[1,2] (MD), normal coordinate analysis,[3] and molecular mechanics[4] (MM) techniques. These techniques require first and sometimes second derivatives of potential energy terms, with most of the computational effort spent in calculating derivatives of internal coordinates. In systems with complicated bond networks and with fairly short range nonbonded interactions, such as Lennard–Jones, derivatives of internal coordinates for chemical bond interactions, especially for three- and four-body types, can take an appreciable fraction of the total computation time. To reduce this effort in MD simulations, Noid et al.[5] use a geo-

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Contract/grant sponsor: U.S. Department of Energy with Lockheed Martin Energy Research Corp.; contract/grant number: DE-AC05-96OR22464

Contract/grant sponsor: Oak Ridge National Laboratory and the Oak Ridge Institute for Science and Education.

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CCC 0192-8651 / 97 / 141804-08

metric statement function approach: internal coordinates and their first derivatives are written in terms of other internal coordinates contained therein. In addition, the constraint that an internal force acting on particles $1, \ldots, n$ does not move the center of mass of the particles involved (a property known as translational invariance) is applied:

$$\left(\frac{\partial V}{\partial q_1} + \frac{\partial V}{\partial q_2} + \cdots + \frac{\partial V}{\partial q_n} \right) = 0 \tag{1}$$

where V is a function of one or more internal coordinates and q is x, y, or z. Improvements to this technique for first derivatives and its extension to second derivatives have been catalogued at length by Tuzun et al.[6] for stretch, bend, torsion, and wag (improper torsion) internal coordinates and potential energy terms.

The first and second derivatives of a potential energy term, $V(\phi)$, where ϕ is an internal coordinate, have the following form:

$$\frac{\partial V(\phi)}{\partial q_i} = \frac{\partial V}{\partial \phi} \frac{\partial \phi}{\partial q_i} \tag{2}$$

$$\frac{\partial^2 V(\phi)}{\partial q_i \, \partial q'_j} = \frac{\partial V}{\partial \phi} \frac{\partial^2 \phi}{\partial q_i \, \partial q'_j} + \frac{\partial^2 V}{\partial \phi^2} \frac{\partial \phi}{\partial q_i} \frac{\partial \phi}{\partial q'_j} \tag{3}$$

and so both first and second derivatives are required for Cartesian second partial derivatives of potential energy terms.

In this article we apply this approach to special four-body interaction types that describe deviation from an equilibrium planar geometry. In the MM2[7] and MM3[8,9] force fields, deviation from an sp^2 equilibrium planar geometry is described by the movement of the central atom (atom 4 in Fig. 1). Out-of-plane bend energies are parameterized by three projected in-plane angles of the type $\theta_{k4'\ell}$ and three out-of-plane bend angles of the type $\theta_{4k4'}$. Several vector identities allow the construction of a small set of intermediates which may be used to calculate all six in- and out-of-plane bend angles and their derivatives.

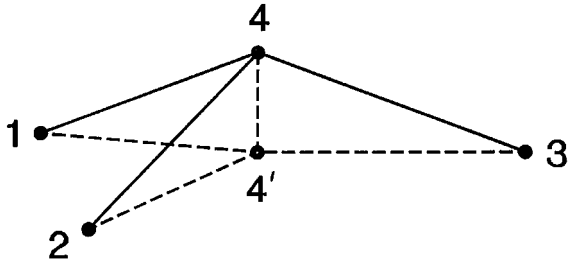

FIGURE 1. In-plane and out-of-plane bend angles. The point 4′ is a projection of point 4 on the 123 plane.

The MM4[10,11] force field is parameterized by three wag (improper torsion) angles 1423, 2413, and 3412, where 1423 denotes the movement of atom 1 out of the 243 plane, with 4 being the central atom. The previous treatment by Tuzun et al.[6] is optimized for a single wag angle. In the MM4 force field, the calculation of the three interlocked wag angles and their first and second derivatives may be optimized in a special manner presented here. The use of internal bend and stretch coordinates and their derivatives renders the treatment of MM2, MM3, and MM4 internal coordinates simple and efficient.

In-Plane and Out-of-Plane Bend Angles

To derive formulas for in-plane and out-of-plane bend angles, the following vector identities prove useful[12]:

$$\mathbf{a} \times \mathbf{a} = \mathbf{0} \tag{4}$$

$$\mathbf{a} \times \mathbf{b} = -\mathbf{b} \times \mathbf{a} \tag{5}$$

$$\mathbf{a} \cdot \mathbf{b} \times \mathbf{c} = \mathbf{b} \cdot \mathbf{c} \times \mathbf{a} = \mathbf{c} \cdot \mathbf{a} \times \mathbf{b} \tag{6}$$

$$\mathbf{a} \times (\mathbf{b} \times \mathbf{c}) = (\mathbf{a} \cdot \mathbf{c})\mathbf{b} - (\mathbf{a} \cdot \mathbf{b})\mathbf{c} \tag{7}$$

$$(\mathbf{a} \times \mathbf{b}) \cdot (\mathbf{c} \times \mathbf{d}) = (\mathbf{a} \cdot \mathbf{c})(\mathbf{b} \cdot \mathbf{d}) - (\mathbf{a} \cdot \mathbf{d})(\mathbf{b} \cdot \mathbf{c}) \tag{8}$$

It is convenient to first define:

$$\begin{aligned} \mathbf{w} &= \mathbf{r}_{12} \times \mathbf{r}_{13} = \mathbf{r}_{23} \times \mathbf{r}_{21} = \mathbf{r}_{31} \times \mathbf{r}_{32} \\ &= (\mathbf{r}_{42} - \mathbf{r}_{41}) \times (\mathbf{r}_{43} - \mathbf{r}_{41}) \\ &= \mathbf{r}_{41} \times \mathbf{r}_{42} + \mathbf{r}_{42} \times \mathbf{r}_{43} + \mathbf{r}_{43} \times \mathbf{r}_{41} \end{aligned} \tag{9}$$

a vector perpendicular to the 123 plane. Here and throughout this article we use the convention:

$$\mathbf{r}_{ij} = \mathbf{r}_j - \mathbf{r}_i \tag{10}$$

It is simple to verify from eqs. (7) and (8) that:

$$\mathbf{r}_{4'k} = \frac{\mathbf{w} \times \mathbf{a}_{4k}}{\mathbf{w} \cdot \mathbf{w}} \tag{11}$$

$$\hat{\mathbf{r}}_{4'k} = \frac{\mathbf{w} \times \mathbf{a}_{4k}}{[\mathbf{w} \cdot \mathbf{w}\mathbf{a}_{4k} \cdot \mathbf{a}_{4k}]^{1/2}} \tag{12}$$

where:

$$\mathbf{a}_{4k} = \mathbf{r}_{4k} \times \mathbf{w} \tag{13}$$

is a vector perpendicular to $\mathbf{r}_{4k}$ and $\mathbf{w}$. Here, and throughout this article, k will denote 1, 2, or 3 and (k, ℓ, m) cyclic permutations of (1, 2, 3). Using eqs. (4)–(8), we then calculate the following intermediates:

$$E = \mathbf{r}_{41} \cdot \mathbf{w} = \mathbf{r}_{42} \cdot \mathbf{w} = \mathbf{r}_{43} \cdot \mathbf{w} = \mathbf{r}_{41} \cdot \mathbf{r}_{42} \times \mathbf{r}_{43} \tag{14}$$

$$C = \mathbf{w} \cdot \mathbf{w} = r_{23}^2 r_{12}^2 - (\mathbf{r}_{21} \cdot \mathbf{r}_{23})^2 \tag{15}$$

$$D = E^2/C \tag{16}$$

$$b_{kk} = \mathbf{a}_{4k} \cdot \mathbf{a}_{4k}/C = r_{4k}^2 - D \tag{17}$$

$$b_{k\ell} = \mathbf{a}_{4k} \cdot \mathbf{a}_{4\ell}/C = \mathbf{r}_{4k} \cdot \mathbf{r}_{4\ell} - D \tag{18}$$

$$f_k = b_{kk}^{1/2} \qquad d_k = 1/f_k \tag{19}$$

and from there the in-plane bend angles:

$$\cos\theta_{k4'\ell} = \hat{r}_{4'k} \cdot \hat{\mathbf{r}}_{4'\ell} = d_k d_\ell b_{k\ell} \tag{20}$$

and out-of-plane bend angles:

$$\cos\theta_{4k4'} = \hat{\mathbf{r}}_{4k} \cdot \hat{\mathbf{r}}_{4'k} = f_k/r_{4k} \tag{21}$$

The vectors $\mathbf{w}$, $\mathbf{a}_{4k}$, $\mathbf{r}_{4k}$, $\mathbf{r}_{4'k}$, and their unit vectors are used as intermediates in the derivation and are not directly calculated, either for the bend angles or their derivatives.

In-Plane and Out-of-Plane Angle Derivatives

To expedite calculation of the first and second derivatives of the in-plane and out-of-plane bend angles, we define:

$$h_{qi}^{(k)} = d_k \frac{\partial f_k}{\partial q_i} \tag{22}$$

Formulas for first and second derivatives of in-plane bend angles begin with:

$$\frac{\partial \cos\theta_{k4'\ell}}{\partial q_i} = d_k d_\ell \frac{\partial b_{k\ell}}{\partial q_i} - \cos\theta_{k4'\ell}\left(h_{qi}^{(k)} + h_{qi}^{(\ell)}\right) \tag{23}$$

$$\begin{aligned}\frac{\partial^2 \cos\theta_{k4'\ell}}{\partial q_i\, \partial q'_j} &= d_k d_\ell \frac{\partial^2 b_{k\ell}}{\partial q_i\, \partial q'_j} - \frac{\partial \cos\theta_{k4'\ell}}{\partial q'_j}\left(h_{qi}^{(k)} + h_{qi}^{(\ell)}\right) \\ &\quad - \frac{\partial \cos\theta_{k4'\ell}}{\partial q_i}\left(h_{q'j}^{(k)} + h_{q'j}^{(\ell)}\right) \\ &\quad - \cos\theta_{k4'\ell}\left(h_{qi}^{(k)} h_{q'j}^{(\ell)} + h_{q'j}^{(k)} h_{qi}^{(\ell)} \right. \\ &\quad \left. + d_k \frac{\partial^2 f_k}{\partial q_i\, \partial q'_j} + d_\ell \frac{\partial^2 f_\ell}{\partial q_i\, \partial q'_j}\right)\end{aligned} \tag{24}$$

where i and j are 1, 2, 3, and are independent. The second derivative formula simplifies for the following special case:

$$\begin{aligned}\frac{\partial^2 \cos\theta_{k4'\ell}}{\partial q_i^2} &= d_k d_\ell \frac{\partial^2 g b_{k\ell}}{\partial q_i^2} - 2\frac{\partial \cos\theta_{k4'\ell}}{\partial q_i}\left(h_{qi}^{(k)} + h_{qi}^{(\ell)}\right) \\ &\quad - \cos\theta_{k4'\ell}\left(2h_{qi}^{(k)} h_{qi}^{(\ell)} + d_k \frac{\partial^2 f_k}{\partial q_i^2} + d_\ell \frac{\partial^2 f_\ell}{\partial q_i^2}\right)\end{aligned} \tag{25}$$

Derivatives with respect to atom 4 coordinates have more complicated formulas which are not presented here. However, it is not required to calculate these derivatives directly in a molecular simulation. Instead, derivatives of the entire potential energy term with respect to coordinates for atoms 1, 2, and 3 are calculated from eqs. (2) and (3). Atom 4 derivatives of the entire potential energy term may then be calculated from translational invariance.

Formulas for derivatives of in-plane bend angles begin with:

$$\frac{\partial \cos\theta_{4k4'}}{\partial q_i} = \frac{1}{r_{4k}} \frac{\partial f_k}{\partial q_i} \qquad (i = \ell, m) \tag{26}$$

$$\frac{\partial \cos\theta_{4k4'}}{\partial q_k} = \frac{1}{r_{4k}}\left(\frac{\partial f_k}{\partial q_k} - \cos\theta_{4k4'} \frac{\partial r_{4k}}{\partial q_k}\right) \tag{27}$$

$$\frac{\partial^2 \cos\theta_{4k4'}}{\partial q_i\, \partial q'_j} = \frac{1}{r_{4k}} \frac{\partial^2 f_k}{\partial q_i\, \partial q'_j} \qquad (i, j = \ell, m) \tag{28}$$

$$\frac{\partial^2 \cos\theta_{4k4'}}{\partial q_i\,\partial q_k} = \frac{1}{r_{4k}}\left(\frac{\partial^2 f_k}{\partial q_i\,\partial q_k} - \frac{\partial \cos\theta_{4k4'}}{\partial q_i}\frac{\partial r_{4k}}{\partial q_k}\right) \quad (i = \ell, m) \tag{29}$$

$$\frac{\partial^2 \cos\theta_{4k4'}}{\partial q_k\,\partial q'_k} = \frac{1}{r_{4k}}\left(\frac{\partial^2 f_k}{\partial q_k\,\partial q'_k} - \frac{\partial r_{4k}}{\partial q_k}\frac{\partial \cos\theta_{4k4'}}{\partial q'_k} - \frac{\partial r_{4k}}{\partial q'_k}\frac{\partial \cos\theta_{4k4'}}{\partial q_k} - \cos\theta_{4k4'}\frac{\partial^2 r_{4k}}{\partial q_k\,\partial q'_k}\right) \tag{30}$$

To use these formulas requires first calculating D and its derivatives, which requires E and C and their derivatives:

$$\frac{\partial E}{\partial q_k} = (\mathbf{r}_{4\ell} \times \mathbf{r}_{4m})_q = (s_\ell - s_4)(u_m - u_4) - (u_\ell - u_4)(s_m - s_4) \tag{31}$$

$$\frac{\partial^2 E}{\partial q_k\,\partial q'_k} = \frac{\partial^2 E}{\partial q_k\,\partial q_\ell} = \frac{\partial^2 E}{\partial q_k\,\partial q_m} = 0 \tag{32}$$

$$\frac{\partial^2 E}{\partial q_k\,\partial s_\ell} = u_m - u_4 \tag{33}$$

$$\frac{\partial^2 E}{\partial q_k\,\partial s_m} = -(u_\ell - u_4) \tag{34}$$

where (q, s, u) refers to cyclic permutations of (x, y, z) and q' is x, y, or z and is independent of q, and:

$$\frac{\partial C}{\partial q_1} = 2\left[(q_1 - q_2)r_{23}^2 - (q_3 - q_2)\mathbf{r}_{21}\cdot\mathbf{r}_{23}\right] \tag{35}$$

$$\frac{\partial C}{\partial q_3} = 2\left[(q_3 - q_2)r_{12}^2 - (q_1 - q_2)\mathbf{r}_{21}\cdot\mathbf{r}_{23}\right] \tag{36}$$

$$\frac{\partial^2 C}{\partial q_1^2} = 2\left[r_{23}^2 - (q_3 - q_2)^2\right] \tag{37}$$

$$\frac{\partial^2 C}{\partial q_1\,\partial v_1} = -2(q_3 - q_2)(v_3 - v_2) \qquad (v = s, u) \tag{38}$$

$$\frac{\partial^2 C}{\partial q_1\,\partial q_3} = 2[(q_1 - q_2)(q_3 - q_2) - \mathbf{r}_{21}\cdot\mathbf{r}_{23}] \tag{39}$$

$$\frac{\partial^2 C}{\partial q_1\,\partial v_3} = 4(q_1 - q_2)(v_3 - v_2) - 2(q_3 - q_2)(v_1 - v_2) \quad (v = s, u) \tag{40}$$

$$\frac{\partial^2 C}{\partial q_3^2} = 2\left[r_{12}^2 - (q_1 - q_2)^2\right] \tag{41}$$

$$\frac{\partial^2 C}{\partial q_3\,\partial v_3} = -2(q_1 - q_2)(v_1 - v_2) \qquad (v = s, u) \tag{42}$$

Formulas for atom 2 derivatives of C are similar to the above expressions; however, once atom 1 and 3 derivatives have been calculated, it takes less computational effort to calculate atom 2 derivatives from translational invariance. From all of these results we may calculate derivatives of D:

$$\frac{\partial D}{\partial q_i} = \frac{1}{C}\left(2E\frac{\partial E}{\partial q_i} - D\frac{\partial C}{\partial q_i}\right) \tag{43}$$

$$\frac{\partial^2 D}{\partial q_i\,\partial q'_j} = \frac{1}{C}\left(2E\frac{\partial^2 E}{\partial q_i\,\partial q'_j} + 2\frac{\partial E}{\partial q_i}\frac{\partial E}{\partial q'_j} - D\frac{\partial^2 C}{\partial q_i\,\partial q'_j} - \frac{\partial C}{\partial q'_j}\frac{\partial D}{\partial q_i} - \frac{\partial C}{\partial q_i}\frac{\partial D}{\partial q'_j}\right) \tag{44}$$

From eq. (32), the second derivative formulas simplify for the following cases:

$$\frac{\partial^2 D}{\partial q_i\,\partial q_j} = \frac{1}{C}\left(2\frac{\partial E}{\partial q_i}\frac{\partial E}{\partial q_j} - D\frac{\partial^2 C}{\partial q_i\,\partial q_j} - \frac{\partial C}{\partial q_j}\frac{\partial D}{\partial q_i} - \frac{\partial C}{\partial q_i}\frac{\partial D}{\partial q_j}\right) \tag{45}$$

$$\frac{\partial^2 D}{\partial q_i\,\partial q_{i'}} = \frac{1}{C}\left(2\frac{\partial E}{\partial q_i}\frac{\partial E}{\partial q_{i'}} - D\frac{\partial^2 C}{\partial q_i\,\partial q_{i'}} - \frac{\partial C}{\partial q_{i'}}\frac{\partial D}{\partial q_i} - \frac{\partial C}{\partial q_i}\frac{\partial D}{\partial q_{i'}}\right) \quad (q \neq q') \tag{46}$$

$$\frac{\partial^2 D}{\partial q_i^2} = \frac{1}{C}\left[2\left(\frac{\partial E}{\partial q_i}\right)^2 - D\frac{\partial^2 C}{\partial q_i^2} - 2\frac{\partial C}{\partial q_i}\frac{\partial D}{\partial q_i}\right] \tag{47}$$

Derivatives of D are required to calculate derivatives of the b's:

$$\frac{\partial b_{kk}}{\partial q_i} = -\frac{\partial D}{\partial q_i} \qquad (i = \ell, m) \tag{48}$$

$$\frac{\partial b_{kk}}{\partial q_k} = 2(q_k - q_4) - \frac{\partial D}{\partial q_k} \tag{49}$$

$$\frac{\partial^2 b_{kk}}{\partial q_i\, \partial q'_j} = -\frac{\partial^2 D}{\partial q_i\, \partial q'_j}$$
$$[i = \ell, m \text{ or } (i = j = k,\ q \neq q')] \tag{50}$$

$$\frac{\partial^2 b_{kk}}{\partial q_k^2} = 2 - \frac{\partial^2 D}{\partial q_k^2} \tag{51}$$

$$\frac{\partial b_{k\ell}}{\partial q_k} = (q_\ell - q_4) - \frac{\partial D}{\partial q_k} \tag{52}$$

$$\frac{\partial b_{k\ell}}{\partial q_\ell} = (q_k - q_4) - \frac{\partial D}{\partial q_\ell} \tag{53}$$

$$\frac{\partial b_{k\ell}}{\partial q_m} = -\frac{\partial D}{\partial q_m} \tag{54}$$

$$\frac{\partial^2 b_{k\ell}}{\partial q_i\, \partial q'_j} = -\frac{\partial^2 D}{\partial q_i\, \partial q'_j}$$
$$[i = m \text{ or } i = j \text{ or } (i = k,\ j = l,\ q \neq q')] \tag{55}$$

$$\frac{\partial^2 b_{k\ell}}{\partial q_k\, \partial q_\ell} = 1 - \frac{\partial^2 D}{\partial q_k\, \partial q_\ell} \tag{56}$$

and, from there, derivatives of f_k:

$$\frac{\partial f_k}{\partial q_i} = \frac{d_k}{2}\frac{\partial b_{kk}}{\partial q_i} \tag{57}$$

$$\frac{\partial^2 f_k}{\partial q_i\, \partial q'_j} = d_k\left(\frac{1}{2}\frac{\partial^2 b_{kk}}{\partial q_i\, \partial q'_j} - \frac{\partial f_k}{\partial q_i}\frac{\partial f_k}{\partial q'_j}\right) \tag{58}$$

Substituting these results into eqs. (22)–(30) yields first and second derivatives of all six in-plane and out-of-plane bend angles. It should be noted that, in this entire process, only three square roots—the f's from eq. (19)—are calculated. The rest of the process consists of multiplications, additions, and a few divisions, which are far less expensive.

Improper Torsion Angles

A wag (also called improper torsion) angle, ω_{4123}, may be visualized as the deviation of atom 1 from the 243 plane, as shown in Figure 1. In the MM4 force field the deviation from a planar configuration (as seen, e.g., around an sp^2 carbon at equilibrium) is parameterized by three wag angles, sin ω_{4123}, sin ω_{4231}, and sin ω_{4312}. Fast formulas for a single wag angle and its derivatives in terms of internal bend and stretch derivatives were recently presented by Tuzun et al.[6]; the treatment of three interlocking wag angles may be optimized further, as we now show.

For the sake of clarity, we now present a derivation for the formulas for a single wag angle 4123. The vector:

$$\mathbf{v} = \hat{\mathbf{r}}_{42} \times \hat{\mathbf{r}}_{43} \tag{59}$$

is perpendicular to the 243 plane and has a magnitude of sin θ_{243}. Let α be the angle made between $\mathbf{r}_{41}$ and $\mathbf{v}$. The improper torsion angle, which is the angle from the 243 plane, is $\pi/2 - \alpha$. Then, from the usual dot product identity we obtain:

$$\sin \omega_{1423} = \cos \alpha = \frac{E}{\sin \theta_{243}} \tag{60}$$

where:

$$E = \hat{\mathbf{r}}_{41} \cdot \hat{\mathbf{r}}_{42} \times \hat{\mathbf{r}}_{43} \tag{61}$$

From eq. (61) it is apparent that each improper torsion angle may be calculated from E:

$$\sin \theta_{243} \sin \omega_{4123} = \sin \theta_{143} \sin \omega_{4231} = \sin \theta_{142} \sin \omega_{4312} = E \tag{62}$$

It may appear at first glance that it matters in which order the satellite atoms are considered, that is, from eq. (5) sin $\omega_{4123} = -\sin \omega_{4132}$. However, in the MM4 force field an atom above its preferred plane yields the same energetics as an atom at the corresponding location below its preferred plane, as expected on physical grounds (i.e., an upturned umbrella acts the same as a downturned umbrella). In the MM4 force field, improper torsional potential energies have the functional form:

$$V(\sin \omega) = k(1 - \cos 2\omega) = 2k \sin^2 \omega \tag{63}$$

and several cross terms involve:

$$\cos \omega = \sqrt{1 - \sin^2 \omega} \tag{64}$$

and so the order of atoms 2 and 3 is irrelevant because these expressions involve even powers of sin ω.

Improper Torsion Angle Derivatives

From eq. (62) it is readily apparent that derivatives of E may be used as intermediates for calculating derivatives of all three improper torsion angles. From eq. (62) and:

$$\hat{\mathbf{r}}_{4k} = \frac{\partial r_{4k}}{\partial q_k}\hat{\mathbf{e}}_q + \frac{\partial r_{4k}}{\partial s_k}\hat{\mathbf{e}}_s + \frac{\partial r_{4k}}{\partial u_k}\hat{\mathbf{e}}_u \tag{65}$$

we obtain:

$$\frac{\partial E}{\partial q_k} = \frac{1}{r_{4k}}\left(-E\frac{\partial r_{4k}}{\partial q_k} + \frac{\partial r_{4\ell}}{\partial s_\ell}\frac{\partial r_{4m}}{\partial u_m} - \frac{\partial r_{4\ell}}{\partial u_\ell}\frac{\partial r_{4m}}{\partial s_m}\right) \tag{66}$$

$$\frac{\partial^2 E}{\partial q_k^2} = -\frac{1}{r_{4k}}\left(2\frac{\partial r_{4k}}{\partial q_k}\frac{\partial E}{\partial q_k} + E\frac{\partial^2 E}{\partial q_k^2}\right) \tag{67}$$

$$\frac{\partial^2 E}{\partial q_k\,\partial q_k'} = -\frac{1}{r_{4k}}\left(\frac{\partial r_{4k}}{\partial q_k'}\frac{\partial E}{\partial q_k} + \frac{\partial r_{4k}}{\partial q_k}\frac{\partial E}{\partial q_k'} + E\frac{\partial^2 r_{4k}}{\partial q_k\,\partial q_k'}\right) \tag{68}$$

$$\frac{\partial^2 E}{\partial q_k\,\partial q_\ell'} = \frac{1}{r_{4k}}\left(-\frac{\partial r_{4k}}{\partial q_k}\frac{\partial E}{\partial q_\ell'} + \frac{\partial^2 r_{4\ell}}{\partial q_\ell'\,\partial s_\ell}\frac{\partial r_{4m}}{\partial u_m} - \frac{\partial^2 r_{4\ell}}{\partial q_\ell'\,\partial u_\ell}\frac{\partial r_{4m}}{\partial s_m}\right) \tag{69}$$

$$\frac{\partial^2 E}{\partial q_k\,\partial q_m'} = \frac{1}{r_{4k}}\left(-\frac{\partial r_{4k}}{\partial q_k}\frac{\partial E}{\partial q_m'} + \frac{\partial r_{4\ell}}{\partial s_\ell}\frac{\partial^2 r_{4m}}{\partial q_m'\,\partial u_m} - \frac{\partial r_{4\ell}}{\partial u_\ell}\frac{\partial^2 r_{4m}}{\partial q_m'\,\partial s_m}\right) \tag{70}$$

From here it is simple to calculate first and second derivatives of the three improper torsion angles:

$$\frac{\partial \sin\omega_{k4\ell m}}{\partial q_k} = \frac{1}{\sin\theta_{\ell 4m}}\frac{\partial E}{\partial q_k} \tag{71}$$

$$\frac{\partial \sin\omega_{k4\ell m}}{\partial q_i} = \frac{1}{\sin\theta_{\ell 4m}}\left(\frac{\partial E}{\partial q_i} - \sin\omega_{k4\ell m}\cos\theta_{\ell 4m}\frac{\partial\theta_{\ell 4m}}{\partial q_i}\right) \quad (i = \ell, m) \tag{72}$$

$$\frac{\partial^2 \sin\omega_{k4\ell m}}{\partial q_k\,\partial q_k'} = \frac{1}{\sin\theta_{\ell 4m}}\frac{\partial^2 E}{\partial q_k\,\partial q_k'} \tag{73}$$

$$\frac{\partial^2 \sin\omega_{k4\ell m}}{\partial q_k\,\partial q_i'} = \frac{1}{\sin\theta_{\ell 4m}}\left(\frac{\partial^2 E}{\partial q_k\,\partial q_i'} - \sin\omega_{k4\ell m}\cos\theta_{\ell 4m}\frac{\partial\theta_{\ell 4m}}{\partial q_i'}\right) \quad (i = \ell, m) \tag{74}$$

$$\frac{\partial^2 \sin\omega_{k4\ell m}}{\partial q_i\,\partial q_j'} = -\cot\theta_{\ell 4m}\left(\frac{\partial\theta_{\ell 4m}}{\partial q_i}\frac{\partial \sin_{k4\ell m}}{\partial q_j'} + \frac{\partial\theta_{\ell 4m}}{\partial q_j'}\frac{\partial \sin\omega_{k4\ell m}}{\partial q_i} + \sin\omega_{k4\ell m}\frac{\partial^2\theta_{\ell 4m}}{\partial q_i\,\partial q_j'}\right) + \frac{1}{\sin\theta_{\ell 4m}}\frac{\partial^2 E}{\partial q_i\,\partial q_j'} - \sin\omega_{k4\ell m}\frac{\partial\theta_{\ell 4m}}{\partial q_i}\frac{\partial\theta_{\ell 4m}}{\partial q_j'} \quad (i, j = \ell, m) \tag{75}$$

Eq. (75) simplifies for the following case:

$$\frac{\partial^2 \sin\omega_{k4\ell m}}{\partial q_i^2} = -\cot\theta_{\ell 4m}\left(2\frac{\partial\theta_{\ell 4m}}{\partial q_i}\frac{\partial \sin_{k4\ell m}}{\partial q_i} + \sin\omega_{k4\ell m}\frac{\partial^2\theta_{\ell 4m}}{\partial q_i^2}\right) + \frac{1}{\sin\theta_{\ell 4m}}\frac{\partial^2 E}{\partial q_i^2} - \sin\omega_{k4\ell m}\left(\frac{\partial\theta_{\ell 4m}}{\partial q_i}\right)^2 \quad (i = \ell, m) \tag{76}$$

To calculate a set of interlocking improper torsion angles, sin ω, and their first and second derivatives with this approach requires no square roots. Quantities that require square roots to calculate, such as sin θ, are assumed to have been calculated in the bend portion of the code and stored for later use. However, cos ω, which is used in several cross terms, requires a square root to calculate.

Results and Discussion

We have presented simple, efficient formulas for first and second derivatives of out-of-plane bend and improper torsion coordinates as implemented in the MM2, MM3, and MM4 force fields. The use of internal bend and stretch coordinates and their derivatives and of several vector identities allows the entire set of in-plane and out-of-plane angles and their derivatives to be calculated from a small number of intermediates. Only three square roots, plus multiplications and additions, are required in the entire calculation. A set of three interlocking wag angles, sin ω, and their derivatives requires only multiplications and additions of bend and stretch intermediates and no square roots. However, certain cross terms, if they are present, require cos ω, which requires a square root to calculate. To use the formulas as presented here requires keeping careful track of bend and stretch interactions; a general bond network method for doing this for several types of internal coordinates, including those treated here, is described elsewhere.[13]

The total simulation time saved by using the formulas presented here depends on the number of sp^2-hybridized carbons in the system and on which algorithm is used for the molecular mechanics calculation. For example, a conjugate gradient calculation would require first derivatives only. To calculate a set of in-plane and out-of-plane potential energies and their first derivatives using the formulas presented here is about six times faster than the same calculation in the MM2-87[14] software (we do not benchmark against MM3 code because the source appears to be unavailable). The speedup factor for the portion of code which computes up to second derivatives (which would be used in calculations using Newton–Raphson methods) is about 20. The reduction in total simulation time, of course, would vary from case to case.

Tuzun et al.[6] recently optimized the calculation of first and second derivatives of a single improper torsion angle. The method presented here for three interlocking improper torsion angles is faster by about 10% for both first and second derivatives and simpler to program. Unfortunately, we could not benchmark against MM4 code because the source appeared to be unavailable.

To compute the first and second Cartesian partial derivatives of $V(\phi)$, where ϕ is an internal coordinate, does not require calculating every first and second derivative of ϕ. It requires only the independent derivatives. These derivatives are combined with V, $dV/d\phi$, and $d^2V/d\phi^2$ as shown in eqs. (2) and (3) to obtain Cartesian partial derivatives of V. Translational invariance and symmetry conditions may then be applied to the entire potential energy term.

To check the correctness and accuracy of our formulas, we derived expressions for each internal coordinate and every first and second derivative (only independent derivatives are reported here) and used MACSYMA[15] to generate corresponding expressions in Cartesian coordinates. For several thousand random sets of coordinates, our formulas and the corresponding MACSYMA expressions were evaluated on an IBM RS6000 workstation in IEEE double precision (about 15 significant figures), our normal working precision. The Cartesian formulas usually satisfied translational invariance to better than 10^{-13}. Our expressions usually agreed with the MACSYMA results to better than 10 figures (or an absolute error of 10^{-12}) and satisfied translational invariance to better than 10^{-14}. The Cartesian expressions were less accurate than our formulas because they had more operations and therefore greater roundoff error.

Conclusions

In this article we present simple, efficient formulas for in-plane and out-of-plane bend and improper torsion coordinates and their first and second derivatives as implemented in the MM2, MM3, and MM4 force fields. The in-plane and out-of-plane formulas are about six times faster (for first derivatives) and about 20 times faster (for second derivatives) than the method used in the MM2-87 software and are no less accurate. The improper torsion formulas are slightly faster than the already efficient formulas of Tuzun et al.[6] (which are optimized for single wag angles) and are easier to program.

First and second derivatives appear to be accurate almost to machine precision or have very small absolute errors; as a consequence of the smaller numbers of operations, they are more accurate than the corresponding Cartesian expressions. Thus, the validity of molecular modeling techniques is limited not by the accuracy of the forces or second derivatives but by other aspects of the algorithm.

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